REMARKS

Claims 1- 74 were pending in the application. Claims 11, 24-41, 44-58, 60-61, 63-65, and 70-74 have been cancelled without prejudice or disclaimer, and claims 1, 7, 8, 10, 14, 15, 22, 23, 67, 68, and 69 have been amended. Accordingly, after the amendments presented herein have been entered, claims 1-10, 12-23, 42, 43, 59, 62 and 66-69 will remain pending.

Support for the amendments to claims 1 and 15 can be found, at least, for example, in claim 11 as originally filed in corresponding international application PCT/GB99/01561, filed May 17, 1999. In addition, claims 1, 7, 8, 10, 14, 15, 22, 23, 67, 68, and 69, and the title of the application, have been amended to correct certain typographical errors. No new matter has been added.

Attached hereto as Appendix A is a marked-up version of the changes made to the claims by the current amendments. Appendix A is captioned "Version With Markings to Show Changes Made." For the Examiner's convenience, the claims as they will be pending after the amendments presented herein have been entered, are set forth herein in Appendix B.

Any amendment to and cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and were done solely to expedite the prosecution of the application. Applicants reserve the right to purse the claims as originally file din this or separate application(s).

Election/Restrictions

Claims 24-41, 44-58, 60-61, 63-65, and 70-74 have been cancelled without prejudice or disclaimer, as directed to non-elected subject matter. Applicants hereby reserve the right to pursue the subject matter of the non-elected claims in one or more divisional applications.

Rejection of Claims 1-10, 12-23, 67, 68, and 69 Under 35 U.S.C. § 102(b) Over Dower et al.

The Examiner has rejected claims 1-10, 12-23, 67, 68, and 69 under 35 U.S.C. § 102(b) as being anticipated by Dower *et al.* (WO 93/06121). The Examiner relies on Dower *et al.* for disclosing "a method for synthesizing libraries of random oligomers." In particular, the Examiner is of the opinion that

> [t]he random oligomers are synthesized on solid supports, or

> particles, but may be cleaved from these supports to provide a soluble library. The oligomers are composed of a sequence of monomers. Each oligomer sequence in the library is unique. The solid supports may be composed of a single particle, or two or more linked particles. A further embodiment relates to the use of an identifier tag to identify the sequence of monomers in the oligomer. The identifier tag, which may be attached directly to the oligomer with or without an accompanying particle, to a linker attached to the oligomer, to the solid support upon which the oligomer is synthesized, or to a second particle attached to the oligomer-carrying particle, may be any recognizable feature that in some way carries the required information, and that is decipherable at the level o one or few solid supports. The solid supports may be joined to the oligomers and the identifier tag by means of one or more linker molecules. The identifier tag an oligonucleotide, or a set of light-addressable compounds, such as fluorescent or phosphorescent compounds that can be photo leached, which compounds are incorporated into the beads or particles on which the oligomers of the oligomer library are synthesized. Such compounds are widely known in the art (Pages 4-7, Pages 22-23, Example I). Figure 3 describes one method of bead functionalization. Figure 4 is a schematic representation of one example of an oligonucleotide tag. Figure 5 illustrates nucleoside phosphoramidites derivatized with photolabile groups. One can readily produced up to 10^{12} different oligomers (pages 11-12).

Applicants respectfully traverse the aforementioned rejection for the following reasons. For prior art reference to anticipate in terms of 35 U.S.C. §102 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed Cir. 1987).

The claimed invention, as set forth in amended independent claim 1, is directed to a method of making a set of oligomer labels. The method includes at least one first or interim step which includes dividing the support into lots, performing a different chemical reaction on each lot of the support so as to either modify that lot of the support or to couple a chemical moiety to that lot of the support, tagging a fraction of each lot of the support with a different label, and combining the lots of the support; and at least one intermediate or final step of dividing the support into lots, performing a different chemical reaction on each lot of the support, so as to either modify that lot of the support or to couple a chemical moiety to that lot of the support, tagging a fraction of each lot of the support with a different cleavable label, ***wherein the label is cleavable to give a charged species for mass spectrometry***, whereby each different cleavable label is linked to a chemical moiety coupled to the support in a different step and forms with that

chemical moiety a labeled compound which is separable from the support, and combining the lots of the support.

Dower *et al.* fail to teach each and every element of the claimed invention. Specifically, Dower *et al.* provide a general stochastic method for synthesizing libraries of random oligomers (see, for example, page 3, line 35 through page 4, line 11). In one embodiment of their invention, Dower *et al.* provide that an identifier tag may be used to identify the sequence of monomers in the oligomers that are synthesized (see page 4, lines 12-20). However, Dower *et al.* fail to teach or suggest the step of using a ***label cleavable to give a charged species for mass spectrometry***. Furthermore, Dower *et al.* fail to teach or suggest the fact that in the at least one intermediate or final step, a fraction of each of the support is tagged with a different cleavable label, where the label is cleavable to give a charged species for mass spectrometry and each different cleavable label is linked to a chemical moiety coupled to the support in a different step and forms with the chemical moiety a labeled compound which is separable from the support. In contrast, Applicants' labeling process allows for cleavable labels to be used as tags and has the benefit of generating charged species, for analysis by mass spectrometry. This property ensures that ions are brought into the vapor phase without the need for added matrix, thus, allowing for further biochemical processes (see page 8, lines 3-10 of Applicants' specification). Therefore, these cleavable labels provide enhanced sensitivity during analysis.

For all of the foregoing reasons, the claimed invention is not anticipated by, nor rendered obvious by, Dower *et al.* Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be reconsidered and withdrawn as applied to the pending claims.

Rejection of Claims 1-23, 42, 43, 59, 62, and 66-69 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1-23, 42, 43, 59, 62, and 66-69 under 35 U.S.C. §103(a) as being unpatentable over Dower *et al.,* in view of Köster (6, 074, 823) and Van Ness *et al.*(WO 97/27331). The Examiner relies on Dower *et al.* for the reasons set forth above and on Köster for disclosing that "in general, when it is the released nucleotide (or ribonucleotide) which is mass modified, the modification should take as few steps as possible to be relatively efficient." In particular, the Examiner is of the opinion that the

> reactions used in adding base protecting groups for oligonucleotide synthesis can also be used to modify the released nucleotide just prior to mass spectrometric analysis. For instance, the amino function of

> adenine, guanine or cytosine can be modified by acylation. The amino acyl function can be, by way of illustration, an acetyl, benzoyl, isobutyryl or anisoyl group. Benzoylchloride, in the presence of pyridine, can acylate the adenine amino group, as well as the deoxyribose (or ribose) hydroxyl groups. As the glycosidic linkage is more susceptible to hydrolysis, the sugar moiety can be selectively deacylated if the acyl reaction was not efficient at those sites (i.e. heterogeneity in molecular weight arising from incomplete acylation of the sugar). The sugar moiety itself can be the target of the mass-modifying chemistry. For example, the sugar moieties can be acylated, tritylated, monomethoxytritylated, etc. Other chemistries for mass-modifying the released nucleotides (or ribonucleotides) will be apparent to those skilled in the art.

Additionally, the Examiner relies on Van Ness *et al.* for disclosing methods and compositions for determining the sequence of nucleic acid molecules. In particular, the Examiner is of the opinion that

> [t]he methods permit the determination of multiple nucleic acid sequences simultaneously. The compounds are used as tags to generate tagged nucleic acid fragments which are complementary to a selected target nucleic acid molecule. Each tag is correlative with a particular nucleotide and is detectable by mass spectrometry. Following separation of the tagged fragments by sequential length, the tags are cleaved from the tagged fragments. The tags are detected by mass spectrometry and the sequence of the nucleic acid molecule is determined.

The Examiner concludes that

> [i]t would have been obvious at the time the invention was made to one of ordinary skill in the art to use mass tag as taught by Van Ness for the method of Dower. The said tag possesses several attributes. It is capable of being distinguished from all other tags. It is capable of being detected when present at 10^{-22} to 10^{-6} mole. It is chemically stable toward all manipulations to which it is subjected; etc. It would possess properties which enhance the sensitivity and specificity of detection (Van Ness pages 26-27).

Applicants respectfully traverse the Examiner's assertion that the proposed combination of the above-cited references renders the claimed invention obvious to the ordinarily skilled artisan at the time of the invention. Reconsideration and withdrawal of the rejection in light of the following discussion are respectfully requested.

As indicated above, the currently pending claims are directed to a method of making a set of oligomer labels. The method includes at least one first or interim step which includes dividing

the support into lots, performing a different chemical reaction on each lot of the support so as to either modify that lot of the support or to couple a chemical moiety to that lot of the support, tagging a fraction of each lot of the support with a different label, and combining the lots of the support; and at least one intermediate or final step which includes dividing the support into lots, performing a different chemical reaction on each lot of the support, so as to either modify that lot of the support or to couple a chemical moiety to that lot of the support, tagging a fraction of each lot of the support with a different cleavable label, whereby the label is joined by a link that is cleavable to give a charge species for mass spectrometry and each different cleavable label is linked to a chemical moiety coupled to the support in a different step and forms with that chemical moiety a labeled compound which is separable from the support, and combining the lots of the support.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success much be founded in the prior art, not in applicant's disclosure." (*Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd,*. 927 F. 2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473 5 USPQ2d 1529, 1531 (Fed. Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the clamed invention. See, *e.g.*, *Carella v. Starlight Archery,* 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.,* 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Applying this standard to the references cited by the Examiner, it is clear that the Examiner has failed to meet the burden of providing evidence of a motivating force sufficient to impel a person of ordinary skill in the art to arrive at Applicants' invention. Specifically, the primary reference of Dower *et al.*only describes a method of synthesizing libraries of random oligomers by exposing the support to one monomer, mixing the support, and then exposing it to another monomer resulting in random oligomers. With respect to labeling, Dower *et al.* teach that their methods involve the use of the same label in each reaction vessel.

The Dower *et al.* reference was distinguished above with regard to the rejection under 35 U.S.C. §102, and those arguments are reiterated here. Moreover, Dower *et al.* do not render the claims of the instant invention obvious and further fail to provide the necessary motivation or a reasonable expectation of success in arriving at the claimed method. Nothing in the teachings of Dower *et al.* would have led the ordinarily skilled artisan to, or suggested to that artisan, the use of tags that are suitable for mass spectrometry. More specifically, the reference neither teaches nor suggests the use of tags that are cleavable to provide charged species for mass spectrometry, thereby eliminating the need for using a matrix for mass spectrometry. Still further, the methods of the invention have advantageous properties not taught or suggested by Dower *et al.*, including the ability to uniquely tag each chemical moiety such that it may be distinguished and uniquely identified in an analytical procedure (see, page 7, lines 26-30), and to generate charged species for analysis by mass spectrometry. This ensures that ions are brought into the vapor phase without the need for added matrix, thus allowing for further biochemical processes (see page 8, lines 3-10).

In fact, Dower *et al.* teach away from the claimed invention by teaching that their method, which is different form the claimed invention, is successful. Thus, because Dower *et al.* teach a successful method of synthesizing and labeling oligomers, an ordinarily skilled artisan would not be motivated to look to other references or to do further research to arrive at the present invention.

The secondary references of Köster and Van Ness *et al.*, relied upon by the Examiner, neither teach nor suggest the claimed invention, nor do they make up for the above-stated deficiencies in the primary reference of Dower *et al.* Accordingly, the proposed combination of references fail to establish a *prima facie* showing of obviousness.

Although the Examiner summarizes the disclosures of Köster and Dower *et al.* at page 5 of the Office Action, the Examiner fails to discuss or proffer any reasoning at all as to why one of ordinary skill in the art would be motivated to combine the two references. Furthermore, the Köster patent is not prior art within the meaning of 35 U.S.C. §103(a) because its publication date (June 13, 2000) is neither prior to the date of invention of the instant application (May 15, 1998) nor more than one year before the filing date of the instant application (May 17, 1999).

The Examiner also cites the Van Ness *et al.* reference as teaching compounds that are used to generate tagged nucleic acid fragments that are complementary to a selected nucleic acid target molecule, that are correlative with a particular nucleotide, and that are detectable by mass spectrometry. The Examiner further indicates that it would be obvious to combine Van Ness *et*

al. with Dower *et al.*, but again provides little reasoning as to why one of ordinary skill in the art would be motivated to combine the references. Moreover, what little reasoning that is given is incorrect.

Van Ness *et al.* teach a method for determining the sequence of nucleic acid molecules by generating tagged nucleic acid fragments that are complementary to a selected target nucleic acid. Van Ness *et al.* also disclose separating the tagged fragments by sequential length, cleaving the tags form the tagged fragments, and detecting the tags by non-fluorescent spectrometry or potentiometry. However, Van Ness *et al.* fail to teach or suggest methods involving at least one intermediate or final step in which a fraction of each of the generated support lots is tagged with a different label, and at least one intermediate or final step in which a fraction of each of the support lots is tagged with a cleavable label that gives a charged species for mass spectrometry.

The process disclosed in Van Ness *et al.* (*e.g.*, see pages 72ff) is essentially a variant of Sanger di-deoxy sequencing, where the four chain terminators include (in one embodiment) different mass tags. However, rather than run four separate chain termination reactions and then four

gel lanes, Van Ness *et al.* can perform all four termination reactions in the same vessel and, after separation of terminated chains by length, the terminal nucleotide can be determined by detecting the terminal mass tag. Thus, the Van Ness *et al.* method attaches a nucleotide-specific label to the terminal nucleotide of a nucleic acid chain, uses that label to determine the terminal nucleotide of each of a series of nucleic acids which must first be separated from each other by length, and then infers the sequence. In contrast, the present invention (and Dower *et al.*) does not necessarily rely on terminal labels (although their use is certainly not excluded), and length separation of nucleotides is not required prior to sequencing.

Furthermore, there is an essential technical incompatibility between the Dower *et al.* and Van Ness methods, because the chain termination which is so essential to Van Ness *et al.* is performed enzymatically by a polymerase off a complementary target. This procedure is very different from the combinatorial method of Dower *et al.* (and of claim 1 presented herein), which involves

division of a support into lots, followed by addition of chemical moieties, and re-mixing of the divided lots.

Therefore, the Examiner's modification of Dower *et al.* by the teaching of Van Ness *et al.* does not make technical sense. In view of this technical incompatibility, how would one of ordinary skill in the art would ensure that the mass-tagged chain-terminated sequences, produced

by enzymatic polymerization off a complementary sequence, would be attached to a support in between steps? Indeed, one of ordinary skill in the art would not be motivated to modify the teachings of Dower *et al.* based on Van Ness *et al.*

In short, the Examiner has taken one document which discloses sequential tagging of nucleotides in a combinatorial method (Dower) and a second document which discloses mass-tagging of nucleic acids (Van Ness), and has combined their teachings without considering the technical sense or compatibility of the combination. This amounts to nothing more than a picking and choosing of claim elements from the prior art, which is indicative of an impermissible hindsight approach to assessing.

In summary, it Applicants' position that the references relied upon by the Examiner alone or in combination fail to teach or suggest the claimed invention. For the foregoing reasons, the section 103(a) rejection is believed to be improper and Applicants respectfully request that it be reconsidered and withdrawn as applied to the pending claims.

CONCLUSION

In view of the foregoing, reconsideration and withdrawal of all the rejections, and allowance of all the pending claims are respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,
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APPENDIX A

MARKED UP VERSION TO SHOW CHANGES MADE

In the Title:

Libraries of Oligomers ~~Labelled~~ Labeled With Different Tags

In the Claims:

1. A method of making a set of ~~labelled~~ labeled compounds, by the use of a support and a set of labels, said method comprising the steps of:

a) at least one first or intermediate step comprising dividing the support into lots, performing a different chemical reaction on each lot of the support so as either to modify that lot of the support or to couple a chemical moiety to that lot of the support, tagging a fraction of each lot of the support with a different label, and combining ~~the~~ said lots of the support, and

b) at least one intermediate or final step comprising dividing the support into lots, performing a different chemical reaction on each lot of the support, so as either to modify that lot of the support or to couple a chemical moiety to that lot of the support, tagging a fraction of each lot of the support with a different cleavable label, whereby each different cleavable label is linked to a chemical moiety coupled to the support in a different step and forms with that chemical moiety a ~~labelled~~ labeled compound which is separable from the support, and combining the said lots of the support.

7. The method of claim 1, wherein each ~~labelled~~ labeled compound comprises a single label and at least one chemical moiety.

8. The method of claim 1, wherein the support is treated to release ~~the~~ said ~~labelled~~ labeled compounds into solution.

10. The method of claim 1, wherein the support has cleavable linkers, wherein each cleavable linker has at least one group for chemical synthesis and another group for ~~labelled~~ labeling.

14. The method of claim 1, wherein the ~~labelled~~ labeled compounds are ~~labelled~~ labeled oligonucleotides.

22. The set of claim 15, wherein the ~~labelled~~ labeled compounds are ~~labelled~~ labeled oligonucleotides.

23. A library consisting of the set of ~~labelled~~ labeled compounds of claim 19.

67. A library consisting of the set of ~~labelled~~ labeled compounds of claim 20.

68. A library consisting of the set of ~~labelled~~ labeled compounds of claim 21.

69. A library consisting of the set of ~~labelled~~ labeled compounds of claim 22.